REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 25-29 and 48-79 are in the case.

I. CLAIM OBJECTIONS

Claims 25, 33 and 46 have been objected to for the reasons detailed on page 2 of the Action. In response, those matters have received attention in the new and amended claims presented herewith. Withdrawal of the claim objections is now respectfully requested.

II. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 28, 33-38 and 41-45 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons detailed on pages 2-4 of the Action. That rejection is respectfully traversed.

In response, the claims have been amended to delete the references to preferred features, and those features are now presented in separate new dependent claims. Claim 28 has been amended so as to define component (a) as selected from an alcoholic herb extract or hydroalcoholic herb extract. The remaining claims have been amended to meet the outstanding objections with respect to antecedent basis.

Withdrawal of the outstanding 35 U.S.C. §112, second paragraph, rejection is now believed to be in order. Such action is respectfully requested.

III. THE OBVIOUSNESS REJECTION

Claims 25-47 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over PDR for Herbal Medicines (1998) and WO 94/25041 to Koniger et al, Derwent Abstract and Machine Translation in view of JP 07-285830 to Ramin, translated as U.S. Patent 5,667,768, and Trimuyadi et al (Conference of the Asian Societies, 2001). That rejection is respectfully traversed.

The invention as claimed is directed to a method of treatment of onychoschizia in a patient in need of such treatment. The method comprises administering to the patient a topical composition comprising (a) at least one herb extract from the genus *Equisetum*, and (b) at least one film forming agent.

The Action asserts that PDR for Herbal Medicines and Koniger describe the use of *Equisetum* for the topical treatment of splitting, brittle fingernail, and Ramin and Trimuyadi suggest the use of chitosan and its derivatives in nail polishes. In particular, the Action suggests that Ramin describes the use of these substances for restructuring and reducing splitting of the nails. In view of this, the Action concludes that it would have been obvious to one of ordinary skill to administer *Equisetum* extract in combination with several other known strengthening agents as a topical application on the nail surface for the treatment of splitting, brittle nails based upon the beneficial teaching provided in the cited references. This position is respectfully traversed.

As discussed in more detail below, none of the cited documents discloses or suggests that an extract from *Equisetum* may be beneficial for the treatment of onychoschizia. Moreover, there is no suggestion in any of the cited documents that a

topical composition comprising such extract would be efficacious in the treatment of onychoschizia.

First, it is noted that, contrary to the Action, onychoschizia is not a generic condition of nail brittleness, but rather a specific and well-characterized pathology of the nails, wherein the distal portion of the nail splits horizontally. This is described in the present specification at paragraphs 0008 and 0012. It is also confirmed by the reference submitted herewith as Enclosure 1.

The cited references contain no disclosure or suggestion of this pathology and none of them would lead one of ordinary skill to believe that *Equisetum* could be beneficial in the treatment of onychoschizia. Moreover, the cited art does not contain any disclosure or suggestion that would motivate the skilled person to believe that the topical treatment of nails with an extract from *Equisetum* may improve brittleness and splitting of the nails.

Referring to PDR for Herbal Medicine (PDR), this document reports that, in folk medicine, *Equisetum* is used, among other applications, for the treatment of "brittle finger nails and loss of hair", but that the efficacy of such use "is not proven". Based on this, a person of ordinary skill would not have been motivated to use *Equisetum* extract to strengthen the nails.

Furthermore, PDR does not suggest that *Equisetum* should be applied **topically** on the nails. Although preparations for external use are described in PDR, there is no disclosure pointing to their use for topical applications on the nails.

Koniger, as acknowledged in the Action, discloses the use of *Equisetum* extracts in the treatment of onychomicosis. Koniger contains no mention of the treatment of

brittle and splitting nails. Onychomicosis and onychoschizia are different and unrelated conditions, and require two completely different treatments. In particular, as described in Enclosure 2 attached hereto, onychomicosis is a fungal infection of the nails, caused by specific microorganisms and its treatment requires the use of antimycotic agents. In this pathology, the nail structure is damaged by the fungi that grow inside the nail and render the nail more fragile. Onychomicosis is never a cause of onychoschizia, but it is frequently a cause of onycholysis, i.e., a detachment of the full nail plate from the nail bed.

In view of the above, since onychomicosis and onychoschizia are quite different and unrelated conditions, requiring completely different treatments, it is clear that one of ordinary skill would not have been motivated to topically use an extract of *Equisetum* to treat onychoschizia based on Koniger. This is further confirmed by the experimental section of the present application.

On page 5 of the Action, it is asserted that Example 10 of the present application constitutes an admission that onychomicosis is "well known in the art to cause splitting and other damage to the nail" since "the applicant included women with this condition in their clinical study". This assertion is respectfully traversed.

As stated above, onychomicosis can cause onycholysis. In Example 10, the study included some subjects that had been previously affected by onychomicosis (as clearly stated in para. 0082). Although this pathology was resolved at the time of inclusion in the study, some subjects still showed onycholysis. As can be seen from the results of this study, after treatment with the claimed composition, no effect was seen in these subjects regarding onycholysis, whereas a definite improvement was recorded

with onychoschizia (a significant improvement ($p<0.001$) was observed compared to untreated nails).

Based on the above, it is clear that there would have been no motivation for one of ordinary skill in the art to arrive at the present invention in light of the cited art. Absent any such motivation, it is clear that a *prima facie* case of obviousness has not been generated in this case. Withdrawal of the obviousness rejection is respectfully requested.

IV. CLAIM AMENDMENTS

Claims 25 to 29 are presented in amended form, and claims 30-47 have been canceled and replaced by new claims 48-79. Claim 28 has been amended to claim alcoholic or hydroalcoholic herb extracts. Support for claims 29 and 48 appears in paragraph 0020 of the application; support for claims 49 and 50 appears in paragraphs 0021 and 0022 of the application; support for claims 55, 57 and 61 appears in former claims 33, 34 and 37, respectively; claims 54, 56, and 60 correspond to former claims 33, 34 and 37, respectively, wherein the reference to preferred embodiments has been eliminated; new claims 51-53 and 58-71 correspond to former claims 30-32 and 35-47, respectively. New claims 72-79 claim preferred features eliminated from the claims upon which they depend. No new matter is entered.

V. PRIORITY CLAIM

It is noted that boxes 12(c)(3) are crossed on the first page of the Action. It is understood that a certified copy of the underlying EP priority document 03076934.3 filed

June 23, 2003 has been forwarded to the US Designated Office. Acknowledgement of receipt of this document is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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Attachments: Enclosures 1 and 2

Enclosure 1

Baran and Dawber's **Diseases of the Nails and their Management**

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stippled aspect of the nail reflects the camera flash and is clearly evident on photography. Alopecia areata may occur in association with both types.

Oral administration of biotin for 6 months resulted in a reduction of longitudinal ridging, thinning and distal notching of the nail plate in two cases of trachyonychia of childhood (Möhrenschlager *et al.* 1998).

A beneficial response following a short course of topically applied 5% 5-fluorouracil cream is anecdotal (Schissel & Elston 1998).

References

Achten, G. & Wanet-Rouard, J.J. (1974) Atrophie unguéale et trachyonychie. *Archives Belges Dermatologique* 30, 201.

Alkiewicz, J. (1950) Trachyonychie. *Annales de Dermatologie et de Syphiligraphie* 10, 136.

Arias, A.M., Yung, C.W., Rendler, S. *et al.* (1982) Familial severe twenty-nail dystrophy. *Journal of the American Academy of Dermatology* 7, 349.

Baran, R. (1981) Twenty-nail dystrophy of alopecia areata. *Archives of Dermatology* 117, 1.

Baran, R. & Dupré, A. (1977) Vertical striated sandpaper nails. *Archives of Dermatology* 113, 1613.

James, W.D., Odom, R.B. & Horm, R.T. (1981) Twenty-nail dystrophy and ichthyosis vulgaris. *Archives of Dermatology* 117, 316.

Leong, A.B., Gange, R.W. & O'Connor, R.D. (1982) Twenty-nail dystrophy (trachyonychia) associated with selective IgA deficiency. *Pediatrics* 100, 418.

Möhrenschlager, M., Schmidt, T., Ring, J. *et al.* (1998) Effects of biotin in trachyonychia of childhood. *Annales de Dermatologie et de Vénéréologie* 125 (Suppl. 1), 176.

Peloro, T.M. & Pride, H.B. (1999) Twenty-nail dystrophy and vitiligo: a rare association. *Journal of the American Academy of Dermatology* 40, 488–490.

Richert, B. & André, J. (1999) Trachyonychia: a clinical and histological study of 22 cases. *Journal of the European Academy of Dermatology and Venereology* 12 (Suppl. 2), S126.

Runne, V. (1980) Twenty-nail dystrophy with knuckle pads. *Zeitschrift für Hautkrankheiten* 55, 901.

Samman, P.D. (1979) Trachyonychia (rough nails). *British Journal of Dermatology* 101, 701.

Schissel, D.J. & Elston, D.M. (1998) Topical 5-fluorouracil treatment for psoriatic trachyonychia. *Cutis* 62, 27–28.

Tosti, A., Fanti, P.A., Morelli, R. *et al.* (1991) Spongiotic trachyonychia. *Archives of Dermatology* 127, 584–585.

Pseudomycotic nail dystrophy (pseudomycotic onychia)

Four cases of isolated pseudomycotic nail dystrophy were studied by Higashi *et al.* (1997). All the fingernails and toenails were simultaneously involved. Clinical features include longitudinal striations, fissuring and scaling of the surface of the nail plate with sometimes a yellow-brown discoloration.

The epithelium of the nail matrix reveals hyperplasia with a granular layer and projections similar to the crest of a wave. Inflammatory cell infiltration is present at the upper dermis of the matrix. The nail plate consists of normally keratinized layers and abnormal ones in stratiform pattern.

These findings differ histologically from that of psoriasis, lichen planus and twenty-nail dystrophy. Because of the inflammatory response of the matrix, Higashi *et al.* (1997) suggest the term 'pseudomycotic onychia'. The significance of isolated pseudomycotic nail dystrophy is not known; however it seems difficult to completely rule out alopecia areata restricted to the nail, a condition where the severe changes are sometimes 'simulating longstanding onychomycosis' (Demis & Weiner 1963). Milligan *et al.* (1988) have reported two cases involving all the digits, associated with vitiligo.

References

Demis, D.J. & Weiner, M.A. (1963) Alopecia universalis, onychodystrophy and total vitiligo. *Archives of Dermatology* 88, 195–201.

Higashi, N., Kume, A., Ueda, K. *et al.* (1997) Clinical and histopathological study of pseudo-mycotic onychia. *Hifu* 39, 469–474.

Milligan, A., Barth, J.H., Graham-Brown, R.A.C. & Dawber, R.P.R. (1988) Pseudo-mycotic nail dystrophy and vitiligo. *Clinical and Experimental Dermatology* 13, 109–110.

Lamellar nail splitting (onychoschizia lamellina)

In this condition, found in 27–35% of normal adult women, the distal portion of the nail splits horizontally (Fig. 2.31). The nail is formed in layers analogous to the formation of scales in the skin; the thin lamellae then break off. Exogenous factors contribute to the defect. It is common in people who carry out a great deal of housework, whose nails are repeatedly soaked in water and then dried. Splitting into layers has been reported in X-linked dominant chondrodysplasia punctata (Happle

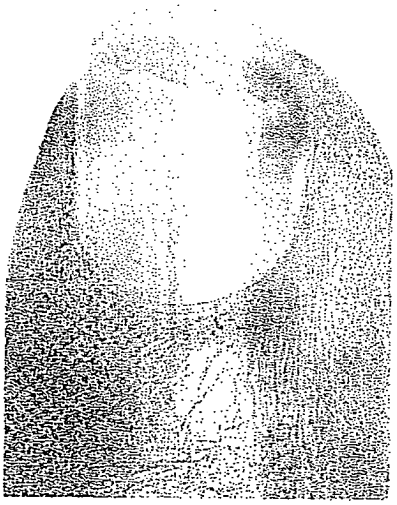
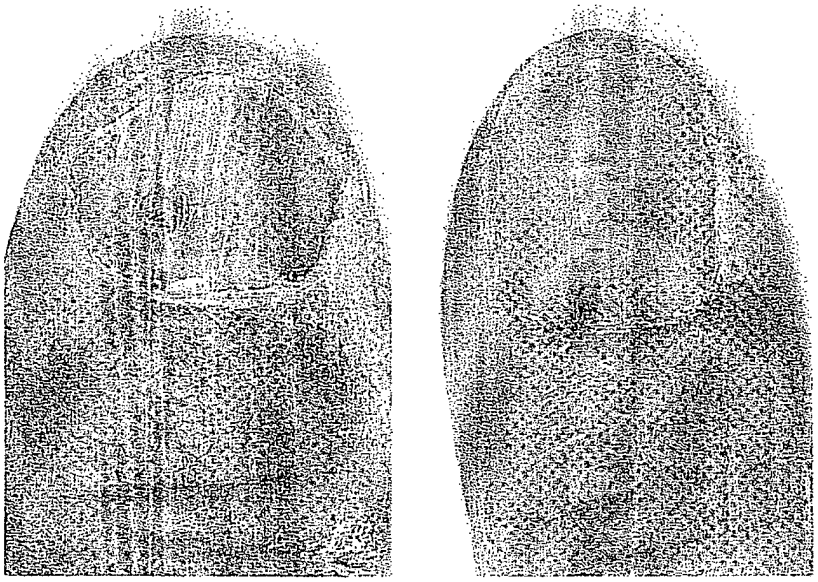


Fig. 2.31 Onychoschizia lamellina (lamellar splitting).



(a) (b) **Fig. 2.32** (a,b) Elkonyxis.

1979) and in polycythaemia vera (Graham-Brown & Homes 1980). In lichen planus, and in psoriasis treated with systemic retinoids, onychoschizia may be seen in the proximal portion of the nail (Baran 1990).

Shelley and Shelley (1984) studied with scanning electron microscopy the distal ends of nails of four women presenting with onychoschizia. The dorsal surface and tip of each nail showed horizontal lamellar separations representing single cell layers. Some cleavage lines extended proximally into the nail plate, revealing remarkable sculptured cell surfaces deep within the plate. These observations indicate that the lamellar splitting of onychoschizia occurs between cell layers. This presumably results from repeated trauma to a nail with diminished adherence between cell layers, secondary to the dissolution of intercellular cement by detergents and nail polish solvent.

Wallis *et al.* (1991) studied the *in vitro* nail changes produced by several organic solvents, detergents, other polar materials, and both acidic and basic solutions. Although other factors may influence onychoschizia, the typical changes can be produced in normal nails after a 21-day challenge of repeated exposure to water followed by dehydration. Scanning electron microscopy demonstrated unattached individual cells in empty spaces in which separation was prominent. The prominent *in vitro* changes from wetting and drying suggest that lamellar dystrophy could be managed by hydration followed by an occlusive topical agent that promotes water retention. Wallis *et al.* (1991) have successfully combined protection from exposure with hydrophilic petrolatum (Aquaphor), as a nail cream applied to the wet nails to maintain a relatively constant level of hydration. α-Hydroxy acids are more than mere moisturizers according to Leyden *et al.* (1995).

References

Baran, R. (1990) Retinoids and the nails. *Journal of Dermatological Treatment* 1, 151–154.

Graham-Brown, R.A.C. & Homes, R. (1980) Polycythaemia rubra vera with lamellar dystrophy of the nails, a report of two cases. *Clinical and Experimental Dermatology* 5, 209.

Happle, R. (1979) X-linked dominant chondrodysplasia punctata. *Humangenetik* 53, 65.

Leyden, J.J., Lavker, R.M., Grove, G. *et al.* (1995) Alpha hydroxy acids are more than moisturizers. *Journal of Geriatric Dermatology* 3 (Suppl. A), 33A–37A.

Shelley, W.B. & Shelley, E.D. (1984) Onychoschizia, scanning electron microscopy. *Journal of the American Academy of Dermatology* 10, 623–627.

Wallis, M.S., Bowen, W.R. & Guin, J.R. (1991) Pathogenesis of onychoschizia (lamellar dystrophy). *Journal of the American Academy of Dermatology* 24, 44–48.

Elkonyxis (Fig. 2.32)

Initially the nail appears punched out at the lunula and subsequently the disorder moves distally with the growth of the nail. It has been described in secondary syphilis, psoriasis, Reiter's syndrome and after trauma. It may be produced by etretinate (Cannara & Gambetti 1990).

Reference

Cannata, G. & Gambetti, M. (1990) Elconyxis, une complication inconnue de l'étrétinate. *Nouvelles Dermatologiques* 9, 251.

Enclosure 2

Baran and Dawber's
Diseases of the Nails and their Management

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In this chapter the onychomycoses are considered in detail, together with a variety of infections occasionally seen in and around the nail apparatus; some infections (see chapter contents above) are discussed, where appropriate, in other chapters.

Onychomycoses occur throughout the world but there are regional differences in incidence. Precise data as to their prevalence have only recently become available and the results again vary from country to country (Baran *et al.* 1999). The results also vary with the method of calculation of the prevalences. For instance Roberts (1992) found that by using a photographic identification method in randomly selected individuals, about 2.3% of subjects in the UK had changes in their nails compatible with onychomycosis. However, larger numbers have been found by direct examination of populations attending dermatologists in the USA and in Finland. Specific groups such as diabetics have also been found to have a higher prevalence than normal individuals (Gupta *et al.* 1998a). Sociocultural and occupational factors play an important part in the increase as well as the spread of organisms such as *Trichophyton rubrum*. In rural areas in Zaire, the incidence was found to be 0.89%, whereas in city dwellers it was 4% in men and 2.8% in women (Vanbreuseghem 1977). Fungal infections of the nails have been reported in 6.5–27% of miners (Götz & Hantschke 1965). Some 1.5% of all patients attending dermatological centres have onychomycosis (Achten & Wanet-Rouard 1981). Between 18% and 40% of all nail disorders are onychomycoses (Pardo-Castello & Pardo 1960; Achten & Wanet-Rouard 1978) and 30% of all dermatomycoses are nail infections (Langer 1957).

Onychomycosis

Fungal infections of the nail apparatus may be classified as superficial, distal or proximal according to the site of fungal invasion (Fig. 4.1). In this chapter a new classification (Baran *et al.* 1998b) is used, which expands on previous schemes to include mycoses involving the whole nail apparatus as well as a new form, endonyx onychomycosis. The appearance of the lesion may provide clues to the likely identity of the infecting organism, although it is seldom possible to identify the species on clinical grounds alone: for instance, irrespective of right or left handedness, unilateral hand involvement is a common feature of dermatophytosis caused by *Trichophyton rubrum*; in such patients both feet are commonly infected (Vazquez *et al.* 1998) (Fig. 4.2). Similarly onychomycosis confined to the fingernails is more suggestive of a *Candida* infection, especially in paronychia and onycholysis, although infections caused by either *Scytalidium dimidiatum* (*Hendersonula toruloidea*) or *S. hyalinum* may both produce identical nail lesions. These observations contribute to the process of making the diagnosis, but this will depend ultimately on the laboratory identification of the fungus. Invasive onychomycosis can also be proved convincingly by histology. A search for infections at other sites such as the hands, feet (soles and webs) or groins, or the scalp in infants, should be instituted when there is a suspicion of onychomycosis. Discoloured dyschromic nail changes caused by fungi are considered in the section on chromonychia (page 89).

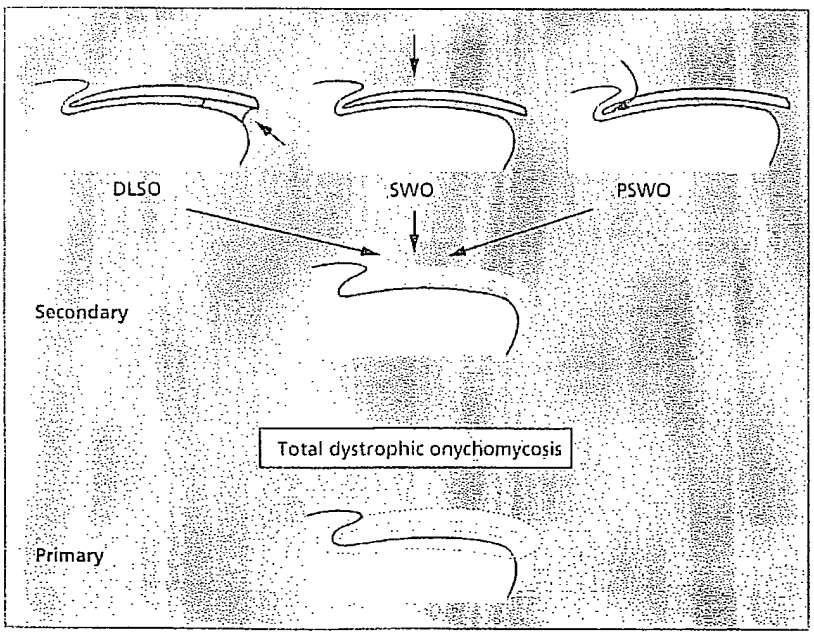
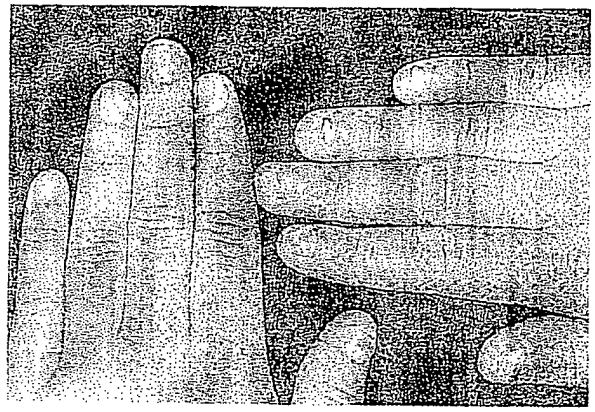
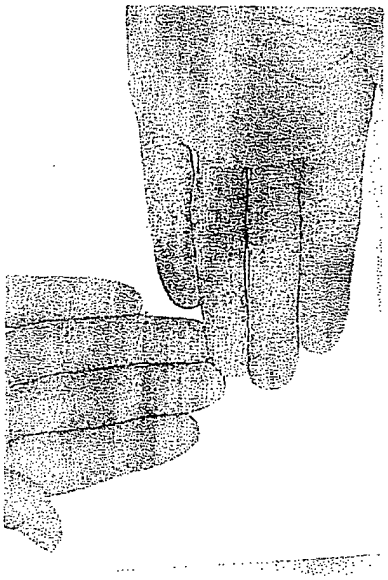


Fig. 4.1 Diagram to show the site of invasion and types of onychomycosis. DLSO, Distal and lateral subungual onychomycosis; EO, endonyx onychomycosis; PSWO, proximal subungual white onychomycosis; SWO, superficial white onychomycosis.



(a)



(b)

Fig. 4.2 (a) Distal and lateral subungual onychomycosis presenting as one hand/two-foot tinea syndrome. (b) Involvement of the palm of the same hand.

Fig. 4.3 Distal and lateral subungual onychomycosis due to *Trichophyton rubrum*.

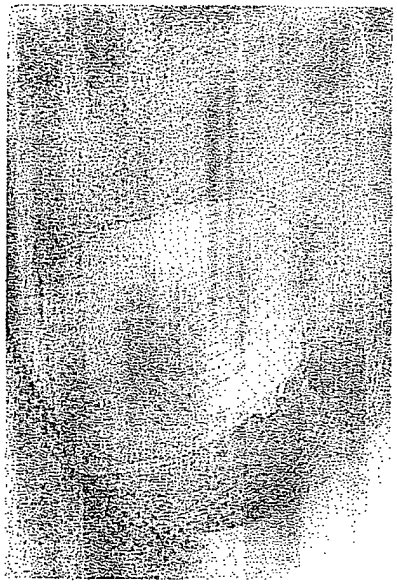


Fig. 4.4 Distal and lateral subungual onychomycosis restricted to the medial edge due to *Trichophyton (mentagrophytes* var.) *interdigitale*.

Distal and lateral subungual onychomycosis (Figs 4.3–4.10)

Primary distal and lateral subungual onychomycosis (Table 4.1)

In this pattern of infection the onychodermal band is disrupted by infection and the fungus reaches the underside of the nail via the hyponychium, the nail bed, or the lateral nail fold where the stratum corneum is invaded. The nail bed infection in distal and lateral subungual onychomycosis (DLSO) caused by *T. rubrum* is the result of the fungus spreading from the plantar (Evans 1998) and palmar surface of the feet and hands, a pattern seen in the one-hand/two-foot tinea syndrome (Daniel *et al.* 1997). The thickened horny layer raises the free edge of the nail plate with disruption of the normal nail plate–nail bed attachment (Baran *et al.* 1998a). The disease spreads proximally and the nail becomes opaque. Fungal invasion leads to orthokeratosis of the nail bed epithelium. In advanced nail disease a more severe inflammatory reaction affects the nail bed with penetration of mononuclear cells and polymorphonuclear leucocytes into the subungual keratin, sometimes mimicking Munro's microabscesses. Parakeratotic foci, often containing inspissated serum, may appear (Haneke 1991). In time, tunnels produced by dermatophytes and containing air, described by Alkiewicz (1948) as a transverse net, appear as opaque streaks in the nail plate. Occasionally, this may be seen more clearly

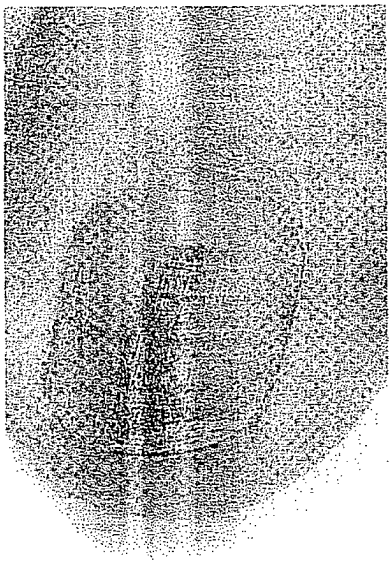


Fig. 4.5 Distal and lateral subungual onychomycosis due to *Trichophyton rubrum nigricans* presenting with longitudinal melanonychia.

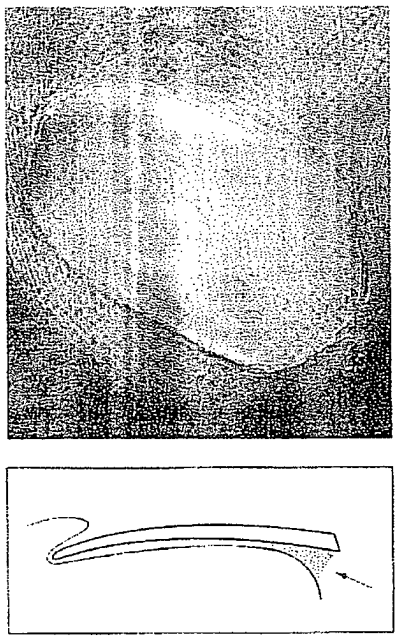


Fig. 4.6 Onycholysis due to *Trichophyton rubrum*.

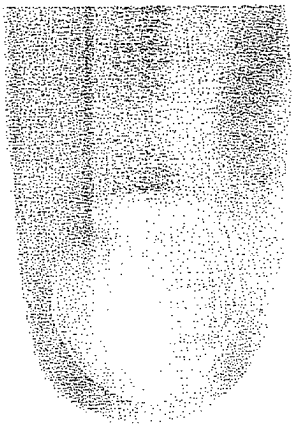


Fig. 4.7 Onycholysis due to *Trichophyton rubrum*.

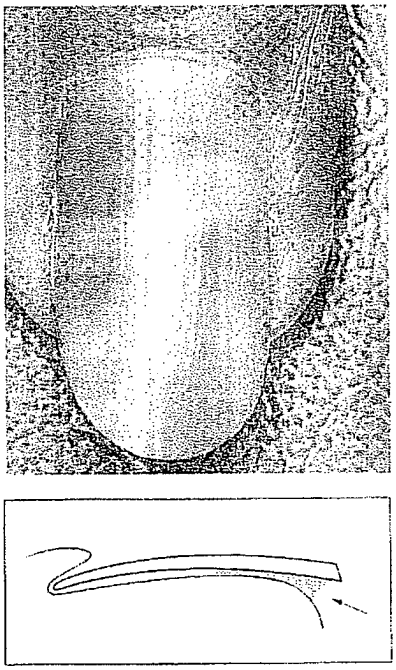
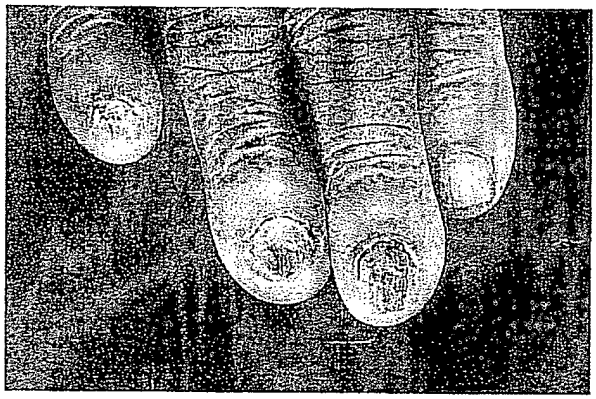


Fig. 4.8 Onycholysis due to *Candida albicans*.

with the aid of a lens, after the nail plate has been treated with cedar oil to render it translucent. Where the network is sufficiently dense, it appears as an opaque white or yellowish zone or streak, a clinical feature often seen in dermatophyte or mould infections. Such lacunae often contain masses of fungi as well as keratin debris and their existence provides a difficult target for treatment as persistence of infection may occur at this site, possibly due to poor drug penetration. Often there is nail invasion in a longitudinal narrow band which follows the ridges of the nail bed. In addition according to Zaias (1972), a variety of microorganisms may coexist in the ecological niche created by an area of onycholysis and these are responsible for colour changes which vary from grey to chestnut brown. Negroni (1976) has reported on nail erythrasma. With progressive infection, the nail becomes friable and eroded at the lateral and distal borders.

The clinical appearances of nail dystrophies caused by different fungi are seldom diagnostic, but there may be some useful and potentially distinctive features apart from the differences in

(a)



(b)

Fig. 4.9 (a) Distal and lateral subungual onychomycosis (DLSO) due to *Scytalidium dimidiatum* in a Caucasian patient. (Courtesy of D. Jones UK.) (b) DLSO associated with paronychia due to *S. dimidiatum*

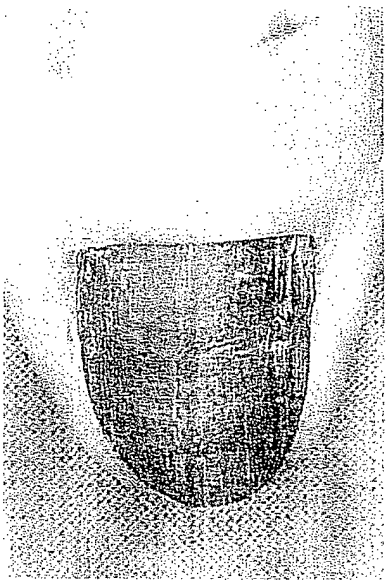


Fig. 4.10 Black nail due to *Candida parapsilosis*. (Courtesy of O. Binet, France.)

Table 4.1 Causes of distal and lateral subungual onychomycosis (DLSO)

Dermatophytes	*Trichophyton rubrum, T. interdigitale, Epidermophyton floccosum, T. schoenleinii, T. tonsurans, T. soudanense, T. erinacei, T. verrucosum, T. concentricum, T. violaceum, M. canis*
Yeasts	*Candida albicans, C. parapsilosis*
Moulds	*Scopulariopsis brevicaulis, Scytalidium dimidiatum, S. hyalinum*

the overall pattern of nail involvement discussed previously. For example hyperkeratosis accompanying onycholysis is a common feature of dermatophyte infections, which are the commonest causes of DLSO, whereas in *Candida* onychomycosis, gross hyperkeratosis is mainly seen in total nail plate involvement in patients with chronic mucocutaneous candidiasis; in other cases of true *Candida* onychomycosis thickening of the nail plate may be minimal. There has been some debate about the role of *Candida* as a cause of DLSO. *Candida* species are said not to produce specific keratinases and therefore they cannot invade the healthy nail plate. There does appear to be a group of patients in whom there is genuine distal and lateral invasion of the nail plate with erosion, confirmed histologically, but without significant thickening. This is mainly seen in women, patients with endogenous or exogenous Cushing's syndrome or those with Raynaud's phenomenon (Hay *et al.* 1988c). It may also occur in some tropical countries. While it is possible that some invasion is secondary to pre-existing onycholysis (see below), this is seldom possible to establish. There is often a distinctive brown- or cinnamon-coloured discoloration of nails, mainly toenails, affected by *Scopulariopsis brevicaulis*. It is caused by the presence of large numbers of pigmented conidia produced *in situ* (Belsan & Fragner 1965). Likewise brown pigmentation appearing as an irregular streak in the nail plate, often at the lateral border of the great toenail, is also a feature of infections caused by *Trichophyton interdigitale* and *T. rubrum* may sometimes present with longitudinal melanonychia (Higashi 1990; Perrin & Baran 1994). In this case the cause of the pigmentation is unknown. The nail dystrophies caused by *Scytalidium dimidiatum* (Fig. 4.9) or *Scytalidium hyalinum* are similar to dermatophyte onychomycosis (Moore 1978; Gugnani *et al.* 1986) and may be found in Caucasians (Jones *et al.* 1985). However, secondary paronychia appears to be

Table 4.2 Organisms found in distal lateral subungual onychomycosis (DLSO) with pre-existing onycholysis.

Dermatophytes	*Trichophyton rubrum, T. interdigitale, Epidermophyton floccosum*
Yeasts	*Candida albicans, C. parapsilosis, C. tropicalis*
Mould	Various species have been reported including *Aspergillus* and *Penicillium*

commoner in fingernail infections and extensive onycholysis may also be a prominent feature of these infections. This may lead to a transverse fracture of the nail plate near the proximal nail fold and subsequent shedding of the distal plate.

Distal and lateral subungual onychomycosis secondary to onycholysis (Table 4.2)

On occasions dermatophytes may be isolated from nails, such as the big toenail, which show idiopathic or primary onycholysis. Davies (1968) reported on 3955 samples of nails infected with *T. rubrum*. Nine per cent of the normal, healthy looking nails were positive for fungus on direct microscopy, culture or both. This was confirmed by Baran and Badillet (1982), who examined 46 samples of normal nails from patients infected in other sites with *T. rubrum* (35 cases), *T. interdigitale* (10 cases) (one patient having a mixed infection), and *Epidermophyton floccosum* (one case). *T. rubrum* was found in the nails of four of these patients, *T. interdigitale* in two and *E. floccosum* in one only. A subsequent control study was carried out on 52 outpatients seeking medical advice for reasons other than big toenail dystrophy. Dermatophytes were isolated from clinically normal big toenails in two patients, *T. rubrum* in one case and *E. floccosum* in the other. In these apparently healthy nails, the fungi were presumably acting as commensals rather than pathogens. However, they are potentially invasive, particularly in nails showing onycholysis, and may be transmitted to a different host. On the fingers, primary onycholysis is more frequently associated with secondary invasion by *Candida* and/or *Pseudomonas*. It is most common in women in whom there is repeated contact with water, soap and detergents. Contrary to the classical pattern of DLSO, which usually starts with distal hyperkeratosis, there is a reversal of the usual order of evolution of each lesion in secondary onychomycosis. For example, in the fingernails onycholysis precedes any subsequent thickening of the distal subungual area, hence the name of DLSO associated with onycholysis. Repeated episodes of friction secondary to rubbing of the nails against shoes or the repeated episodic trauma incurred during running or jogging may also create an area of traumatic onycholysis where microorganisms are also potentially but not invariably pathogenic. A variety of fungi not normally considered pathogenic may be isolated from dystrophic nails, particularly in the elderly (English & Atkinson 1974). The usual clinical pattern of nail involvement most closely resembles DLSO. Hyperkeratosis and brown or green discoloration are common and the toenails are most commonly affected. The organisms isolated may include *Aspergillus* species such as *A. terreus* or *A. versicolor*, *Acremonium* spp., *Penicillium* spp. and *Pyrenochaeta unguium hominis* (Punithaligam & English 1975). As these organisms do not appear to be able to break down keratin, it is assumed that they are colonists of dystrophic or abnormal nails. It is however difficult to be certain that they are not contributing to the nail dystrophy. There is some evidence that some of these species (e.g. *Acremonium* spp.) produce perforating organs, specialized hyphal structures usually associated with hair invasion, analogous to those seen in dermatophytosis. Other non-dermatophyte fungi invading nails such as *S. brevicaulis* can be demonstrated by electron microscopy inside keratinized cells (Achren *et al.* 1979). *Scytalidium* species, pathogenic in humans, produce keratinases.

Other yeasts may also be isolated from the same site. These include *Candida* species such as *C. guilliermondii*. As with the moulds discussed above, it is assumed that they are secondary invaders. The distinction between nail pathogens and opportunistic organisms which inhabit nails under abnormal conditions is a tenuous one. As has been seen above, even the dermatophytes can be secondary invaders (Baran & Badillet 1983). Likewise *S. brevicaulis* is often merely a colonist.

The clinical significance of nail invasion or colonization by fungi, which are not normally pathogenic, needs to be carefully considered in the light of laboratory findings such as the results of nail biopsy. It is likely that organisms which colonize nails may play a more destructive role if the host's immune defences or the nail matrix is altered by disease or another infection. Equally their removal may simply be 'academic' if the nail dystrophy remains after antifungal therapy.

Superficial onychomycosis

Superficial white onychomycosis (Figs 4.11–4.13, Table 4.3)

Superficial white onychomycosis (SWO) is fairly rare and is normally confined to the toenails.

Here the surface of the nail plate is the initial site of invasion. The causative organisms produce a clinical picture of small superficial white patches with distinct edges (Zaias 1966). These later coalesce and may gradually cover the whole nail, hence the term leuconychia trichophytica (mycotica). The chalky white surface becomes roughened and the texture softer than normal. The appearance has been likened to 'paper-bark' (McAleer 1981), the affected nail plate crumbles easily and old lesions acquire a yellowish colour. The upper surface of the nail plate is the primary site of the fungal invasion. This type of nail invasion is caused by *T. interdigitale (mentagrophytes)* in more than 90% of the cases. Using epi-illumination microscopy the individual white flakes representing colonies of *T. interdigitale* can be observed clearly. Patches of SWO are not uncommonly

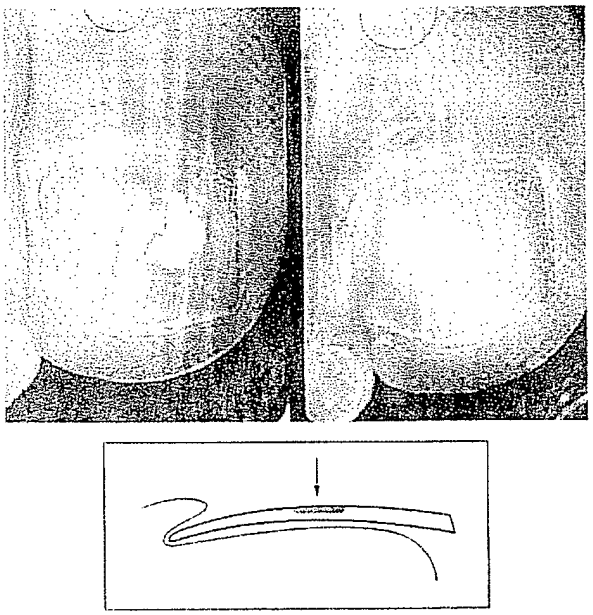


Fig. 4.11 Superficial white onychomycosis due to *Trichophyton interdigitale*. (a) Before scraping. (b) After superficial scraping.

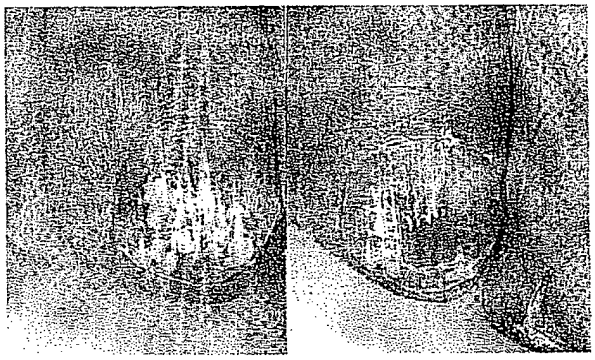


Fig. 4.12 Superficial white onychomycosis due to *Aspergillus* spp. (a) Before scraping. (b) After scraping.

seen in areas where the nail is occluded, for instance by an overlying adjacent toe. Infections caused by non-dermatophytes such as *Aspergillus terreus*, *Fusarium oxysporum* or *Acremonium* spp. are more often seen in patients in a tropical or subtropical environment. *Candida albicans* has occasionally been isolated in infants (Zaias 1990a).

Superficial black onychomycosis (Fig. 4.14)

A similar pattern of nail plate invasion and dystrophy may be caused by dematiaceous or black fungi. These are rare but the following have been described as possible causes: *S. dimidiatum* (Badillet 1988; Meisel & Quadripur 1992); *T. rubrum* (Badillet 1988).

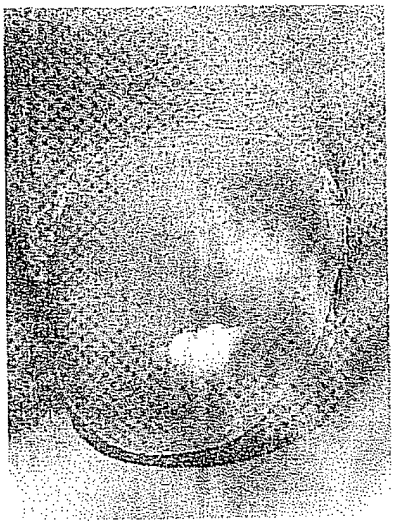


Fig. 4.13 Superficial white onychomycosis associated with distal and lateral subungual onychomycosis due to *Trichophyton interdigitale*.

Table 4.3 Causes of superficial white onychomycosis (SWO).

Dermatophytes	*Trichophyton interdigitale* (*Microsporum persicolor*, *T. rubrum** and *T. equinum*)
Yeasts	*Candida albicans* (only in infants, Zaias 1990a)
Moulds	*Acremonium* and *Fusarium* spp., *Aspergillus terreus*

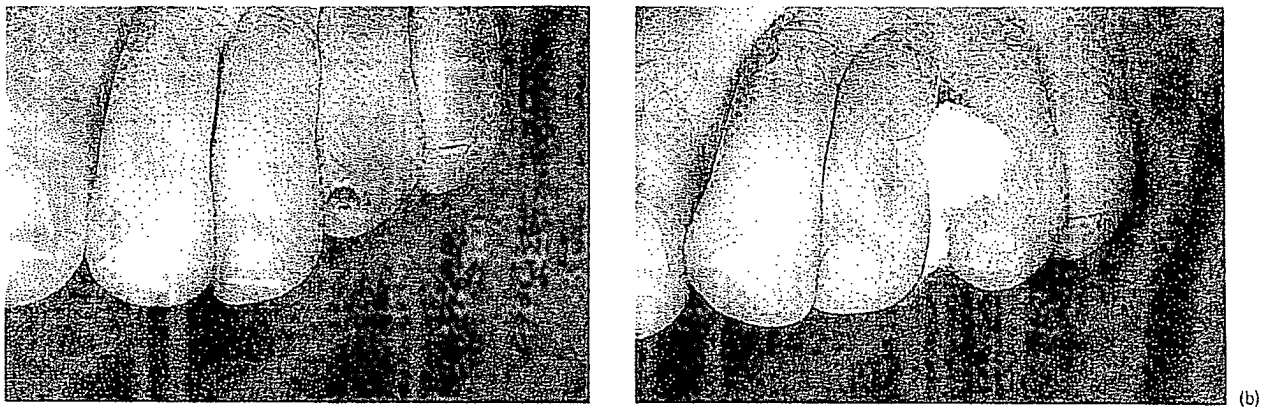
* In this case fungal elements are found deep in the nail plate.

Variants of superficial white onychomycosis

In HIV-infected patients SWO is not rare in finger or toenails and is due to *T. rubrum* (Chapter 6). However, here the pattern of infection is different, as there is often proximal subungual infection as well (see below).

Endonyx onychomycosis (Fig. 4.15)

In endonyx onychomycosis (EO) infections of the fingernails due to the dermatophytes which cause endothrix scalp infections may present with less nail plate thickening, but the plate is pitted and the distal margin covered with lamellar splits (Kalter & Hay 1988). These changes have been studied in detail by Tosti *et al.* (1999) and shown to consist of areas of superficial nail plate invasion but with deep penetration, and fungal hyphae are seen within the nail plate. The nail surface has lamellar-like splits and the end of the nail plate is often friable and split. However, hyperkeratosis is minimal and dense opacification is unusual. These changes are typical of invasion caused by *Trichophyton soudanense* but similar changes have been seen with *T. violaceum*.



(a) (b)

Fig. 4.14 Superficial black onychomycosis due to *Scytalidium dimidiatum*. (a) Before scraping (Courtesy of G. Badillet, France.) (b) After superficial scraping.

Fig. 4.15 Endonyx onychomycosis due to *Trichophyton soudanense*.

Proximal subungual onychomycosis

Proximal white subungual onychomycosis (Figs 4.16–4.18)

Proximal white subungual onychomycosis (PWSO) is rare and affects both fingernails and toenails. This clinical pattern of nail invasion is very rare. The causative organisms penetrate via the proximal nail fold, the stratum corneum of which is the primary site of the fungal invasion. When reaching the matrix the fungus invades the undersurface of the nail plate. A white spot appears from beneath the proximal nail fold and, although it is confined initially to the lunula area, when the white spot moves distally, it still remains in the same layer of the nail plate. The fungus has to invade more distal parts of the matrix to get entrapped in the deeper layers of the nail plate. This is sometimes accompanied by slight discomfort. This pattern may also be seen where there is a recurrence of nail infection in an incompletely treated nail.

This type of nail invasion is usually caused by *T. rubrum*; but *T. megnini*, *T. schoenleinii* or *E. floccosum* may be seen.

Recently a rapidly developing form of PWSO has been recorded in patients with AIDS. Here the infection may spread rapidly under the nail from the proximal margin of all the finger and toenails (Dompmartin *et al.* 1990). Histopathology shows that the entire nail plate is infiltrated with fungi, which are lying in a longitudinal parallel arrangement. However, the picture is complicated in that other surfaces such as the superior aspect of the plate and the distal or lateral margins may also be involved.

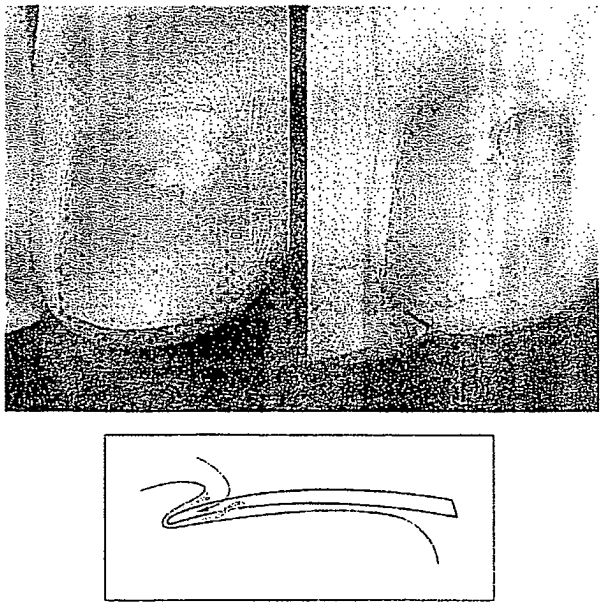


Fig. 4.16 (a) Proximal white subungual onychomycosis. (b) Biopsy restricted to the nail plate.

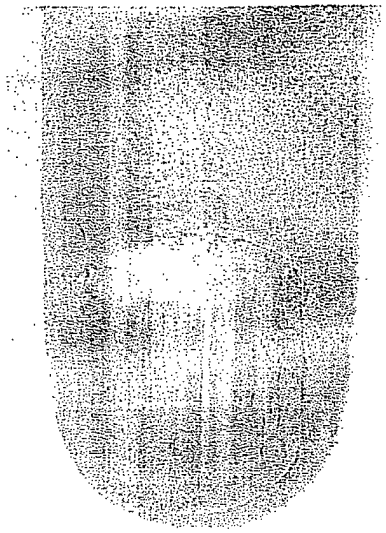


Fig. 4.17 Proximal white subungual onychomycosis with dystrophic keratin of the superficial nail plate.

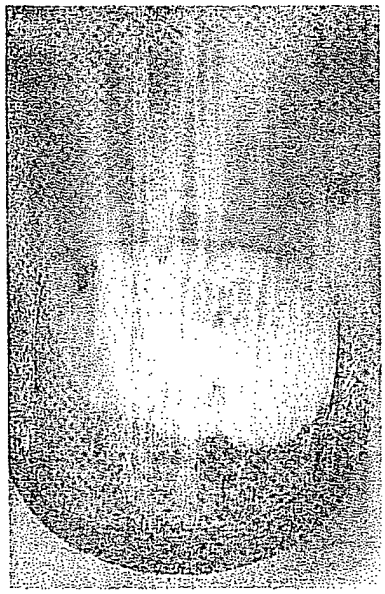
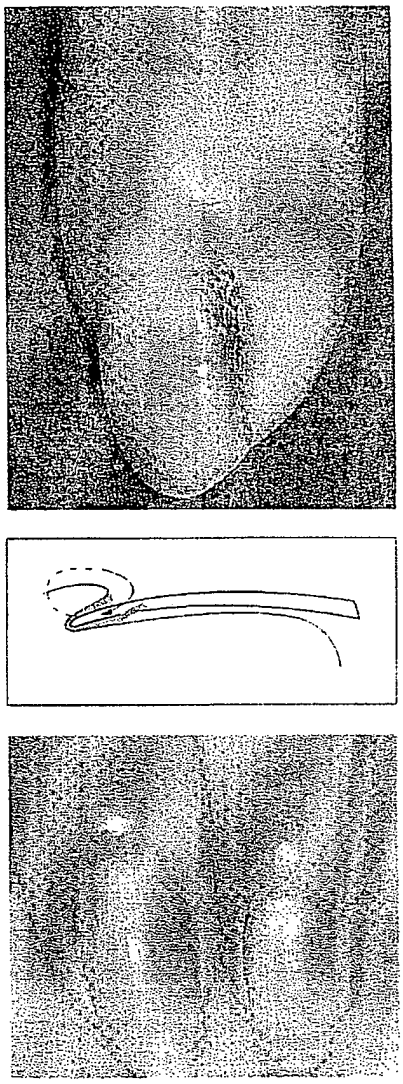


Fig. 4.18 Proximal white subungual onychomycosis in AIDS.

Possibly because of the rapid spread these patients do not show much nail thickening (Weismann *et al.* 1988).

Proximal subungual onychomycosis secondary to paronychia (Fig. 4.19)

Paronychia is observed mainly in adult women and affects particularly the index, middle finger and thumb of the dominant hand. Frequent manual work with carbohydrate-containing foods and moisture, maceration, occlusion, hyperhidrosis and acrocyanosis favour the disease. In children, finger sucking is a

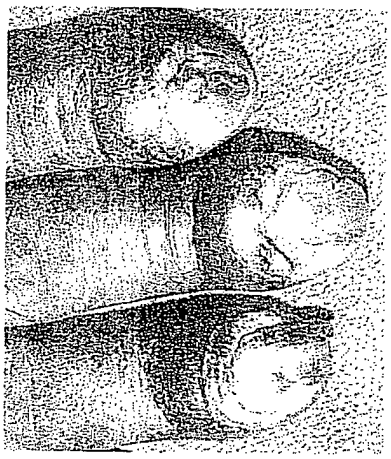


(a)

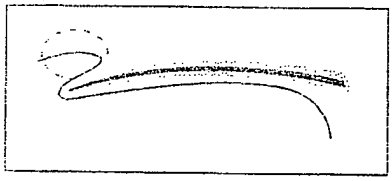
(b)

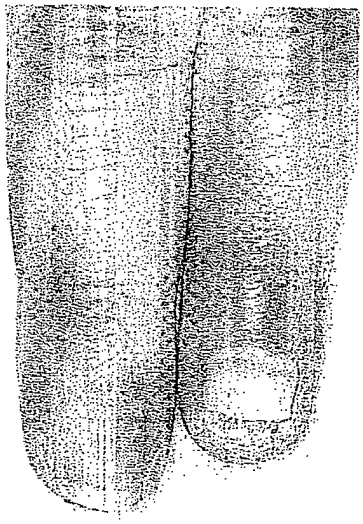
(c)

Fig. 4.19 (a) Proximal subungual onychomycosis secondary to chronic paronychia. (b) Early stage—normal nails. (c) Gross lateral periungual inflammation and swelling with early nail plate involvement of the lateral edges. *(continued p. 135)*

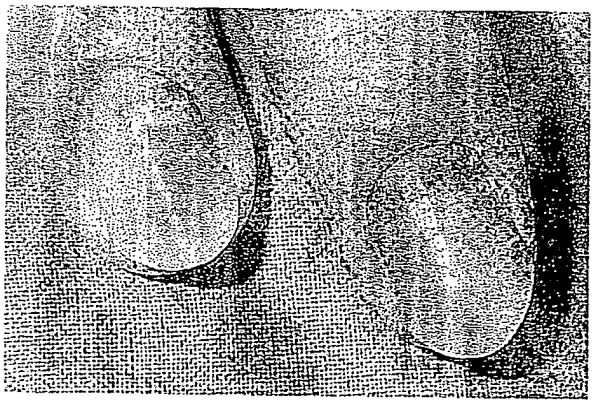


(d)





(e)



(f)

cause of paronychia (Stone & Mullins 1968). Diabetes mellitus and other hormonal disturbances and drugs such as corticosteroids, cytotoxics and antibiotics may exacerbate *Candida* paronychia. The first step in the development of chronic paronychia is mechanical infection or chemical trauma that produce cuticle damage. At that time the epidermal barrier of the ventral aspect of the proximal nail fold is destroyed and the area is suddenly exposed to a variety of environmental hazards. Irritants and allergens may then produce an inflammatory reaction of the nail fold and nail matrix, which interferes with the normal nail growth. Usually the nail fold inflammation affects the lateral portion of the matrix leading to nail plate deformity on the same side, appearing as irregular transverse ridging or a dark narrow strip down one or both lateral borders of the nail.

The thickened free end of the erythematous proximal nail fold becomes rounded, retracted and loses the ability to form a cuticle. The disease tends to run a protracted course interrupted by subacute exacerbations due to secondary *Candida* and bacterial infection with the formation of a small abscess in the space formed between the proximal nail fold and the nail plate. *Candida* spp. and bacteria are frequently isolated from beneath the proximal nail fold in patients with chronic paronychia (Daniel *et al.* 1996).

Depending on the major aetiological factors involved, chronic paronychia can be classified into the following types (Tosti & Piraccini 1997):

1 Contact allergy (topical drug ingredients, rubber, etc.) (Tosti *et al.* 1991).

2 Food hypersensitivity (a variety of immediate contact dermatitis due to foods).

3 *Candida* hypersensitivity (a similar reaction to that suggested in some patients with recurrent vaginitis).

4 Irritative reaction (irritative chronic paronychia may subsequently acquire a secondary hypersensitivity and develop chronic food hypersensitivity paronychia and/or *Candida* hypersensitivity paronychia).

5 *Candida* paronychia. True *Candida* paronychia is uncommon in temperate climates except in patients with chronic mucocutaneous candidiasis and HIV infection. In this condition proximal nail fold inflammation is usually associated with proximal onycholysis or onychomycosis due to *Candida*, which can be isolated both from the proximal nail fold and clipping of the affected nail plate. In contrast to *Candida* infection, non-dermatophyte moulds such as *Fusarium* (Fig. 4.19e) may produce subacute paronychia accompanied by proximal white onychomycosis especially in immunocompromised individuals (Baran *et al.* 1997). In *Fusarium* infection subsequent disseminated spread of the organism to affect other sites in the severely neutropenic patients may be preceded by a type of cellulitis proceeding from the nail fold (Rabodonirina *et al.* 1994).

Fig. 4.19 *(cont'd)* (d) Chronic paronychia with total dystrophic onychomycosis. (e) Chronic leuconychia with paronychia due to *Fusarium* infection. (f) Transverse green stripe due to *Pseudomonas* infection corresponding to exacerbation of the paronychia.

Scopulariopsis brevicaulis may be responsible for identical features with a white or yellow discoloration of the nail plate (Tosti *et al.* 1996a). Proximal subungual onychomycosis (PSO) may also be associated with marked periungual inflammation and black discoloration of the lunula region due to *Aspergillus niger* (Tosti & Piraccini 1998).

On rare occasions other infections may involve the nail fold causing a form of paronychia. Amongst the fungi, the agents of sporotrichosis and, less commonly, chromoblastomycosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and mycetoma may involve this area.

6 Bacterial paronychia. Bacteria may play a role in the pathogenesis of paronychia associated with *Candida* (see above). In addition, *Staphylococcus aureus* may cause an acute paronychia in an otherwise healthy patient. This generally arises as a result of an acute nail fold infection or whitlow and the nail fold may become swollen with subsequent discharge of pus via this area. Alternatively chronic paronychia caused by *S. aureus* is not infrequently seen in patients with skin disease, such as psoriasis or eczema, affecting the nail fold. Generally these are difficult to distinguish clinically from *Candida* infections. *Pseudomonas* infection of the proximal nail fold may produce transverse green stripes on the nail corresponding to exacerbations of the paronychia (Shellow & Koplon 1968) (Fig. 4.19f).

7 Paronychia caused by foreign bodies (Stone *et al.* 1964, 1975).

Total dystrophic onychomycosis (Figs 4.20–4.26)

Total dystrophic onychomycosis (TDO) represents the most advanced form of all the four previous types described above, especially DLSO. The nail crumbles and disappears leaving a thickened and abnormal nail bed which usually retains fragments of nail plate. All 20 nails may be involved in chronic generalized dermatophytosis (Hadida *et al.* 1966; Boudghène-Stambouli & Mérad-Boudia 1998). In the new form of total nail dystrophy observed in patients with AIDS, infection appears to have spread from under the proximal nail fold (PSO) but this has not been established in all cases. The dorsum of the nail plate may also be involved. The term acute TDO might be appropriate for this type of infection. In contrast to secondary TDO, primary TDO is observed only in patients suffering from chronic mucocutaneous candidiasis (CMC) or in other immunodeficiency states (Table 4.4) (Coleman & Hay 1997). *Candida* invasion rapidly involves all the tissues of the nail apparatus. The thickening of the soft tissues results in a swollen distal phalanx more bulbous than clubbed. The nail plate is thickened, opaque and yellow-brown in colour. Hyperkeratotic areas secondary to *Candida* invasion may develop in skin adjacent to the nail. Oral candidiasis is generally present in these patients. This syndrome, which usually occurs in childhood or infancy, recurs despite treatment. Dual or sole infection with dermatophytes may occur in patients with CMC.

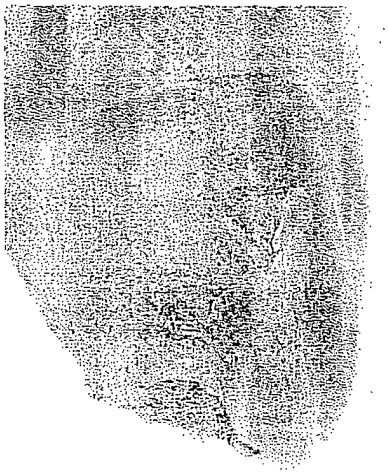


Fig. 4.21 Total dystrophic onychomycosis due to *Trichophyton rubrum*.

Fig. 4.22 Total dystrophic onychomycosis due to *Trichophyton rubrum*. (Courtesy of S. Goettmann-Bonvalot, France.)

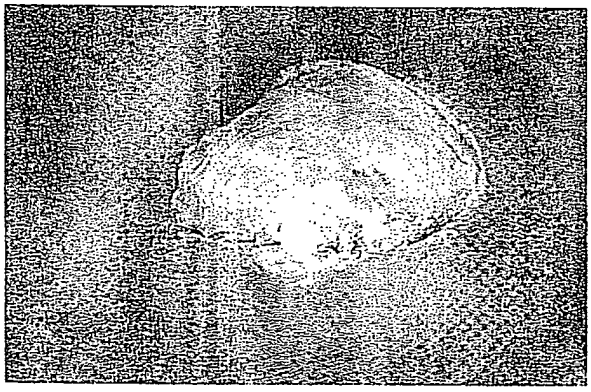


Fig. 4.20 Total dystrophic onychomycosis due to *Scopulariopsis brevicaulis*.